FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 4121-125

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/857902

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE99/03972	8 December 1999	10 December 1998

TITLE OF INVENTION

SPERMATOGENESIS PROTEIN

APPLICANT(S) FOR DO/EO/US

Zdenek Sedlacek and Annemarie Poustka

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).***(Unsigned)**

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☒ A small entity statement. Small entity status is claimed.

16. ☐ Other items or information: EPO Search Report and disk with sequence listings in Patentin 2.1,

NOTE: This application is being filed with an unsigned Oath or Declaration under the provisions of 37 CFR § 1.53 in order that applicants may secure a filing date of June 8, 2001. Upon receipt of a "Notice to File Missing Parts - Filing Date Granted," a executed Declaration and Power of Attorney will be forwarded. The undersigned agent affirmatively states that she has been duly authorized and appointed to file this application on behalf of the applicants and applicants' assignees, and that the Declaration and Power of Attorney to be filed hereafter will confirm the undersigned agent's authorization and appointment. Applicants are considered a small entity and assignee Deutsches Krebsforschungszentrum is also considered a small entity within the meaning of 37 CFR § 1.9.

09/857902 JC03 Rec'd PCT/PTO 08 JUN 2001

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO ..... $860.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... $0.00 No International preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... $0.00 Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... $1000.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $0.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	11-20 =	0	X **$18.00**	$	
Independent Claims	1- 3 =	0	X **$80.00**	$	
Multiple dependent claim(s) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				860.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 430.00	
SUBTOTAL =				$ 430.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 Months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 430.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEE ENCLOSED =				$ 430.00	
				Amount to be: refunded	$
				Charged	$

a. ☒ A check in the amount of $430.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-3284. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not yet been met, a petition to revive (37 CFR 1.127(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Steven J. Hultquist
Intellectual Property/Technology Law
P. O. Box 14329
Research Triangle Park, NC 27709

MARIANNE FUIERER
Registration No. 39,983

#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:			
Applicants:	**Sedlacek, et al.**	**Docket No.:**	**4121-125**
Application No.:	**09/857,902**		
Date Filed:	**June 8, 2001**		
Title:	**SPREMATOGENESIS PROTEIN**		

EXPRESS MAIL CERTIFICATE

I hereby certify that I am mailing the attached documents to the Commissioner for Patents on the date specified, in an envelope addressed to the Commissioner for Patents, Washington, D.C., 20231 and Express Mailed under the provisions of 37 CFR 1.10.

Lu Ann Brown
Lee Ann Brown

July 13, 2001
Date

EL831358157US
Express Mail Label Number

EL831358157US

PRELIMINARY AMENDMENT IN U.S. PATENT APPLICATION NO. 09/857,902

Commissioner for Patents
Washington, DC 20231

07/20/2001 MNGUYEN 00000021 09857902
01 FC:966 36.00 OP

Sir:

Prior to examination of the above-identified patent application, please amend the application, as follows:

In the Specification

On page 2, please amend the first, second, third and fourth paragraphs to read as follows:

The present invention is based on applicant's findings that the gene XAP-5 localized in X-chromosomal manner has a partner gene which is localized in autosomal fashion and is expressed in many tissues. For example, the expression can be found in the testicles, it being here especially strong in spermatogenesis, in particular in the stages of primary and secondary spermatocytes as well as the round spermatocytes. The partner gene is referred to as X5L and is localized in the human genome on chromosome 6 in the region 6pter. Applicant isolated and characterized X5L on the PAC clone LLNLp 704K12294Q13. The DNA comprises a coding sequence and an intron and results in an about 1.6 kb long cDNA. It codes for an approximately 37 kD long spermatogenesis protein comprising 325 amino acids and referred to as X5L protein *(cf.* figures 1, 2 (SEQ ID NO: 1, 2, and 3) and 5, 6). Applicant also found out that mutations in the X5L protein may impair spermatogenesis.

According to the invention applicant's findings are utilized to provide a spermatogenesis protein (X5L protein) comprising the amino acid sequence of figure 1 (SEQ ID NO: 2) or an amino acid sequence differing therefrom by one or several amino acids, a homology of at least 70 % being present between the latter amino acid sequence and the amino acid sequence of figure 1 (SEQ ID NO: 2).

The expression "an amino acid sequence differing by one or several amino acids comprises any amino acid sequence coding for an X5L protein and having a homology of at least 80 % with respect to that of figure 1 (SEQ ID NO: 2). The amino acid sequence may differ from that of figure 1 (SEQ ID NO: 2)by additions, deletions, substitutions and/or inversions of individual amino acids. In

particular, the amino acid sequence may be that of figure 3 (SEQ ID NO: 5)..

Another subject matter of the present invention is a nucleic acid which codes for an X5L protein. The nucleic acid may be an RNA or a DNA, e.g. a cDNA. A DNA is preferred which comprises the following:

(a) The DNA of figure 1 (SEQ ID NO: 1)or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of figure 1 (SEQ ID NO: 1)and coding for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1 (SEQ ID NO: 2), or

(b) a DNA related to the DNA of (a) via the degenerated genetic code.

On page 3, please amend the second paragraph to read as follows:

The expression "a DNA differing by one or more base pairs" comprises any DNA sequence coding for an X5L protein, which hybridizes with the DNA of figure 1 (SEQ ID NO: 1) and codes for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1 (SEQ ID NO: 2). The DNA sequence may differ from the DNA of figure 1 by additions, deletions, substitutions and/or inversions of individual base pairs. In particular, the DNA sequence may be that of figures 2 to 4 (SEQ ID NO: 3, 4, 5 and 6). The expression "hybridization" refers to hybridization under common conditions, in particular at 20°C below the melting point of the DNA sequence.

On page 7, please amend the first, second, third and fourth paragraphs to read as follows:

Figure 1 shows the DNA (SEQ ID NO: 1) and amino acid sequences of a spermatogenesis protein (SEQ ID NO: 2) according to

the invention which comprises 325 amino acids (X5L protein). The DNA sequence is a human cDNA.

Figure 2 shows the sequences of a genomic DNA coding for an X5L protein (SEQ ID NO: 3). The DNA originates from the human genome. The cDNA of figure 1 starts at the -739 base pair. An intron is present between base pairs 828 and 1129. A polyadenylation site is found at the 2658 base pair.

Figure 3 shows the DNA (SEQ ID NO: 4) and amino acid sequences of an X5L protein (SEQ ID NO: 5) comprising 334 amino acids. The DNA sequence is a mouse cDNA.

Figure 4 shows the sequence of a genomic DNA coding for an X5L protein. The DNA originates from the mouse genome. The cDNA of figure 3 starts at the 445 base pair of figure 4 (A) (SEQ ID NO: 6). An intron is present between the base pairs 492-1232 of figure 4 (A). An intron is present between base pairs 1-1136 of figure 4(B) (SEQ ID NO: 7). A polyadenylation sequence is found at the 2306 base pair of figure 4(B).

In the Claims

Please amend claims 1-11 to read as follows:

1. A spermatogenesis protein, comprising the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence differing therefrom by one or more amino acids, wherein a homology of at least 80% exists between the latter amino acid sequence and that of SEQ ID NO: 2.

2. The spermatogenesis protein according to claim 1, comprising the amino acid sequence of SEQ ID NO: 5.

3. A DNA coding for the spermatogenesis protein, comprising:

(a) the DNA of SEQ ID NO: 1 or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of SEQ ID NO: 1 and coding for a spermatogenesis protein whose amino acid sequence has a homology of at least 80% to that of SEQ ID NO: 2, or

(b) a DNA related to the DNA from (a) via the degenerated genetic code.

4. The DNA according to claim 3, wherein the latter DNA is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7.

5. An expression plasmid, comprising the DNA according to claim 3.

6. A transformat, containing the expression plasmid according to claim 5.

7. A method of producing a spermatogenesis protein, comprising the culturing of the transformat according to claim 6 under suitable conditions.

8. Antibodies directed against the spermatogenesis protein according to claim 1.

9. Use of the spermatogenesis protein according to claim 1 for studying or influencing spermatogenesis.

10. Use according to claim 9, wherein the influence of spermatogenesis comprises its activation or inhibition.

11. Use according to claim 9, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.

Please add the following new claims 12-24.

12. An expression plasmid, comprising the DNA according to claim 4.

13. A transformat, containing the expression plasmid according to claim 13.

14. A method of producing a spermatogenesis protein, comprising the culturing of the transformat according to claim 13 under suitable conditions.

15. Antibodies directed against the spermatogenesis protein according to claim 2.

16. Use of the spermatogenesis protein according to claim 2.

17. Use of the spermatogenesis DNA according to claim 3.

18. Use of the spermatogenesis DNA according to claim 4.

19. Use according to claim 16, wherein the influence of spermatogenesis comprises its activation or inhibition.

20. Use according to claim 17, wherein the influence of spermatogenesis comprises its activation or inhibition.

21. Use according to claim 18, wherein the influence of spermatogenesis comprises its activation or inhibition.

22. Use according to claim 16, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.

23. Use according to claim 17, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.

24. Use according to claim 18, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.

REMARKS

A marked-up version of amended paragraphs in the specification and amended claims are included herewith in Appendix A.

Fees Payable

Four new dependent claims are added beyond the number for which a fee has previously been paid, resulting in an added claims fee of $36.00.

A check in the amount of $36.00 is submitted herewith in payment of the added claims fee. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

It is requested that the examination and prosecution of this application proceed on the basis of claims 1-24 setforth hereinabove.

Respectfully submitted,

Marianne Fuierer
Registration No. 39,983
Attorney for Applicants

INTELLECTUAL PROPERTY/
TECHNOLOGY LAW
P. O. Box 14329
Research Triangle Park, NC 27709
Phone: (919) 419-9350
Fax: (919) 419-9354
Attorney File: 4121-125

APPENDIX A

In the Specification

On page 2, please amend the first, second, third and fourth paragraphs to read as follows:

The present invention is based on applicant's findings that the gene XAP-5 localized in X-chromosomal manner has a partner gene which is localized in autosomal fashion and is expressed in many tissues. For example, the expression can be found in the testicles, it being here especially strong in spermatogenesis, in particular in the stages of primary and secondary spermatocytes as well as the round spermatocytes. The partner gene is referred to as X5L and is localized in the human genome on chromosome 6 in the region 6pter. Applicant isolated and characterized X5L on the PAC clone LLNLp 704K12294Q13. The DNA comprises a coding sequence and an intron and results in an about 1.6 kb long cDNA. It codes for an approximately 37 kD long spermatogenesis protein comprising 325 amino acids and referred to as X5L protein *(cf.* figures 1, 2 (SEQ ID NO: 1, 2, and 3) and 5, 6). Applicant also found out that mutations in the X5L protein may impair spermatogenesis.

According to the invention applicant's findings are utilized to provide a spermatogenesis protein (X5L protein) comprising the amino acid sequence of figure 1 (SEQ ID NO: 2) or an amino acid sequence differing therefrom by one or several amino acids, a homology of at least 70 % being present between the latter amino acid sequence and the amino acid sequence of figure 1 (SEQ ID NO: 2).

The expression "an amino acid sequence differing by one or several amino acids comprises any amino acid sequence coding for an X5L protein and having a homology of at least 80 % with respect to that of figure 1 (SEQ ID NO: 2). The amino acid sequence may differ from that of figure 1 (SEQ ID NO: 2)by additions, deletions,

substitutions and/or inversions of individual amino acids. In particular, the amino acid sequence may be that of figure 3 (SEQ ID NO: 5).

Another subject matter of the present invention is a nucleic acid which codes for an X5L protein. The nucleic acid may be an RNA or a DNA, e.g. a cDNA. A DNA is preferred which comprises the following:

(a) The DNA of figure 1 (SEQ ID NO: 1)or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of figure 1 (SEQ ID NO: 1)and coding for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1 (SEQ ID NO: 2), or

(b) a DNA related to the DNA of (a) via the degenerated genetic code.

On page 3, please amend the second paragraph to read as follows:

The expression "a DNA differing by one or more base pairs" comprises any DNA sequence coding for an X5L protein, which hybridizes with the DNA of figure 1 (SEQ ID NO: 1) and codes for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1 (SEQ ID NO: 2). The DNA sequence may differ from the DNA of figure 1 by additions, deletions, substitutions and/or inversions of individual base pairs. In particular, the DNA sequence may be that of figures 2 to 4 (SEQ ID NO: 3, 4, 5 and 6). The expression "hybridization" refers to hybridization under common conditions, in particular at 20°C below the melting point of the DNA sequence.

On page 7, please amend the first, second, third and fourth paragraphs to read as follows:

Figure 1 shows the DNA (SEQ ID NO: 1) and amino acid sequences of a spermatogenesis protein (SEQ ID NO: 2) according to

the invention which comprises 325 amino acids (X5L protein). The DNA sequence is a human cDNA.

Figure 2 shows the sequences of a genomic DNA coding for an X5L protein (SEQ ID NO: 3). The DNA originates from the human genome. The cDNA of figure 1 starts at the -739 base pair. An intron is present between base pairs 828 and 1129. A polyadenylation site is found at the 2658 base pair.

Figure 3 shows the DNA (SEQ ID NO: 4) and amino acid sequences of an X5L protein (SEQ ID NO: 5) comprising 334 amino acids. The DNA sequence is a mouse cDNA.

Figure 4 shows the sequence of a genomic DNA coding for an X5L protein. The DNA originates from the mouse genome. The cDNA of figure 3 starts at the 445 base pair of figure 4 (A) (SEQ ID NO: 6). An intron is present between the base pairs 492-1232 of figure 4 (A). An intron is present between base pairs 1-1136 of figure 4(B) (SEQ ID NO: 7). A polyadenylation sequence is found at the 2306 base pair of figure 4(B).

In the Claims

Please amend claims 1-11 to read as follows:

1. A spermatogenesis protein, comprising the amino acid sequence of [fig. 1] SEQ ID NO: 2 or an amino acid sequence differing therefrom by one or more amino acids, wherein a homology of at least 80% exists between the latter amino acid sequence and that of [fig. 1] SEQ ID NO: 2.

2. The spermatogenesis protein according to claim 1, comprising the amino acid sequence of [fig. 3] SEQ ID NO: 5.

3. A DNA coding for the spermatogenesis protein [according to claim 1], comprising:

(a) the DNA of [fig. 1] SEQ ID NO: 1 or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of [fig. 1] SEQ ID NO: 1 and coding for a spermatogenesis protein whose amino acid sequence has a homology of at least 80% to that of [fig. 1] SEQ ID NO: 2, or

(b) a DNA related to the DNA from (a) via the degenerated genetic code.

4. The DNA according to claim 3, wherein the latter DNA is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 7 [that of fig.2, fig. 3, or fig. 4].

5. An expression plasmid, comprising the DNA according to claim 3 [or 4].

8. Antibodies directed against the spermatogenesis protein according to claim 1 [or 2].

9. Use of the spermatogenesis protein according to claim 1 [or 2 or a DNA according to claim 3 or 4] for studying or influencing spermatogenesis.

SEQUENCE PROTOCOL

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Asn Arg Leu Arg Glu Glu Leu Arg Gln Glu Trp Glu Ala Lys Arg Glu
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Lys Val Lys Gly Glu Glu Val Glu Ile Thr Phe Ser Tyr Trp Asp Gly
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Spermatogenesis Protein

The present invention relates to a spermatogenesis protein, a DNA coding for such a protein and a method of producing such a protein. The invention also relates to antibodies directed against the protein and to the use of the DNA and the protein for studying or influencing spermatogenesis.

Spermatogenesis is referred to as the formation of sperms in mammals or humans. This formation takes place in the testicles. During spermatogenesis, in particular the pachytene stage of meiosis, the X and Y chromosomes accumulate and form what is called a sex body. The X and Y chromosomes are present inactively therein, i.e. they are not transcribed.

It has now turned out that some of the genes of the X and Y chromosomes have partner genes which are localized in autosomal manner. They are expressed *inter alia* in the testicles, so that their gene products have compensatory functions in spermatogensis as regards the corresponding inactivated genes of the X and Y chromosomes.

Influencing spermatogenesis is still a major problem. This is in particular due to the fact that spermatogenesis is not understood in detail.

It is thus the object of the present invention to provide a product by which spermatogenesis can be studied and possibilities can optionally be shown by means of which spermatogenesis can be influenced.

According to the invention this is achieved by the subject matters defined in the claims.

The present invention is based on applicant's findings that the gene XAP-5 localized in X-chromosomal manner has a partner gene which is localized in autosomal fashion and is expressed in many tissues. For example, the expression can be found in the testicles, it being here especially strong in spermatogenesis, in particular in the stages of primary and secondary spermatocytes as well as the round spermatocytes. The partner gene is referred to as X5L and is localized in the human genome on chromosome 6 in the region 6pter. Applicant isolated and characterized X5L on the PAC clone LLNLp 704K12294Q13. The DNA comprises a coding sequence and an intron and results in an about 1.6 kb long cDNA. It codes for an approximately 37 kD long spermatogenesis protein comprising 325 amino acids and referred to as X5L protein (cf. figures 1, 2 and 5, 6). Applicant also found out that mutations in the X5L protein may impair spermatogenesis.

According to the invention applicant's findings are utilized to provide a spermatogenesis protein (X5L protein) comprising the amino acid sequence of figure 1 or an amino acid sequence differing therefrom by one or several amino acids, a homology of at least 70 % being present between the latter amino acid sequence and the amino acid sequence of figure 1.

The expression "an amino acid sequence differing by one or several amino acids comprises any amino acid sequence coding for an X5L protein and having a homology of at least 80 % with respect to that of figure 1. The amino acid sequence may differ from that of figure 1 by additions, deletions, substitutions and/or inversions of individual amino acids. In particular, the amino acid sequence may be that of figure 3.

Another subject matter of the present invention is a nucleic acid which codes for an X5L protein. The nucleic acid may be an RNA or a DNA, e.g. a cDNA. A DNA is preferred which comprises the following:

(a) The DNA of figure 1 or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the

DNA of figure 1 and coding for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1, or

(b) a DNA related to the DNA of (a) via the degenerated genetic code.

The expression "a DNA differing by one or more base pairs" comprises any DNA sequence coding for an X5L protein, which hybridizes with the DNA of figure 1 and codes for an X5L protein whose amino acid sequence has a homology of at least 80 % to that of figure 1. The DNA sequence may differ from the DNA of figure 1 by additions, deletions, substitutions and/or inversions of individual base pairs. In particular, the DNA sequence may be that of figures 2 to 4. The expression "hybridization" refers to hybridization under common conditions, in particular at 20°C below the melting point of the DNA sequence.

The DNAs of figures 1 to 4 were deposited as h-X5L-c, h-X5L-g, m-X5L-c and m-X5L-g on November 26, 1998 with DSMZ (*Deutsche Sammlung von Mikroorgansmen und Zellkulturen* [Germany-type collection of microorganisms and cell cultures]) under DSM 12550, DSM 123553, DSM 12552 and DSM 12551, respectively.

A DNA according to the invention may be present as such or in combination with any other DNA. In particular, a DNA according to the invention which codes for an X5L protein may be present in an expression vector. A person skilled in the art is familiar with examples thereof. In the case of an expression vector for *E. coli* these are e.g. pGEMEX, pUC derivatives, pGEX-2T, pET3b, and pQE-8. For the expression in yeast e.g. pY100 and Ycpad1 have to be mentioned, while e.g. pKCR, pEFBOS, cDM8 and pCEV4 have to be indicated for the expression in animal cells. The bacculovirus expression vector pAcSGHisNT-A is particularly suitable for the expression in insect cells.

The person skilled in the art knows suitable cells to express the DNA according to the invention which is present in an expression vector. Examples of such cells comprise the *E. coli* strains HB101, DH1, x1776, JM101, JM 109, BL 21 and SG 13009, the yeast strain *Saccharomyces cerevisiae* and the animal cells L, NIH 3T3, FM3A, CHO, COS, Vero and HeLa as well as the insect cells sf9.

The person skilled in the art knows how to insert the DNA according to the invention in an expression vector. He is also familiar with the fact that this DNA can be inserted in combination with a DNA coding for another protein or peptide, so that the DNA according to the invention can be expressed in the form of a fusion protein.

Moreover, the person skilled in the art knows conditions of culturing transformed or transfected cells. He also knows methods of isolating and purifying the protein or fusion protein expressed by the DNA according to the invention.

Another subject matter of the present invention is an antibody directed against an above protein or fusion protein. Such an antibody may be made by common methods. It may be polyclonal or monoclonal. For its production it is favorable to immunize animals - in particular rabbits or chickens for a polyclonal antibody and mice for a monoclonal antibody - with an above (fusion) protein or with fragments thereof. Further boosters of the animals may be made with the same (fusion) protein or with fragments thereof. The polyclonal antibody may then be obtained from the serum or egg yolk of the animals. For obtaining the monoclonal antibody animal spleen cells are fused with myeloma cells.

Another subject matter of the present invention is a kit. Such a kit comprises one or more of the following components:

(a) a DNA according to the invention,
(b) a spermatogenesis protein according to the invention (X5L protein),

(c) an antibody according to the invention, and
(d) common auxiliary agents, such as carriers, buffers, solvents, controls, etc.

One or more representatives of the individual components may be present each. As to the individual terms reference is made to the above statements. They apply here correspondingly.

The present invention enables the study of spermatogenesis. An X5L protein may be detected by means of an antibody according to the invention. A relationship may be established between an X5L protein and processes occurring in spermatogenesis. Furthermore, an autoantibody directed against this protein may be detected with an X5L protein. Both detections may be made by common methods, in particular a Western blot, an ELISA, an immunoprecipitation or by immunofluorescence. In addition, the organization and expression of the gene coding for an X5L protein may be detected with a nucleic acid according to the invention. This detection may be made as usual, in particular in a Southern blot, by *in situ* hybridization or by PCR.

Besides, the present invention is also suitable to take steps for inhibiting, or increasing the activity of, an X5L protein in persons. An X5L protein may be inhibited by means of an antibody according to the invention. On the other hand, the amount of an X5L protein in persons can be increased using an X5L protein, in particular after linkage to a protein which is not considered foreign by the body, e.g. transferrin or BSA. The same can also be achieved correspondingly with a nucleic acid according to the invention, in particular a DNA which is controlled by a constitutive promoter or a promoter inducible in certain tissues and after its expression results in the provision of an X5L proteins in the person or in certain tissues, e.g. testicles.

Thus, the present invention relates to means for studying spermatogenesis and influencing it by regulating it. The latter comprises both its activation and its inhibition. In

particular, the present invention provides means serving for diagnosing and treating disorders of spermatogenesis.

Brief Description of the Drawings.

Figure 1 shows the DNA and amino acid sequences of a spermatogenesis protein according to the invention which comprises 325 amino acids (X5L protein). The DNA sequence is a human cDNA.

Figure 2 shows the sequences of a genomic DNA coding for an X5L protein. The DNA originates from the human genome. The cDNA of figure 1 starts at the -739 base pair. An intron is present between base pairs 828 and 1129. A polyadenylation site is found at the 2658 base pair.

Figure 3 shows the DNA and amino acid sequences of an X5L protein comprising 334 amino acids. The DNA sequence is a mouse cDNA.

Figure 4 shows the sequence of a genomic DNA coding for an X5L protein. The DNA originates from the mouse genome. The cDNA of figure 3 starts at the 445 base pair of figure 4(A). An intron is present between the base pairs 492-1232 of figure 4(A). An intron is present between base pairs 1-1136 of figure 4(B). A polyadenylation sequence is found at the 2306 base pair of figure 4(B).

Figure 5 shows the detection of mRNA of an X5L protein in tissues.

Figure 6 shows the detection of mRNA of an X5L protein in testicles. The presence of such an mRNA is limited to tubuli (figure 6(A)). At a cellular level, mRNA of an X5L protein is present in the stages of primary and secondary spermatocytes (stars) and the round spermatocytes (RS). Mature sperms are characterized by (MS) and spermatogoniums are marked by (arrowheads). Sertoli cells (arrows) and Leydig cells (L) have no mRNA of an X5L protein.

The present invention is explained by the below examples.

Example 1: Detection of mRNA of an X5L protein in tissues

(A)

RNA blots of human tissues such as pancreas, suprarenal medulla, thyroid gland, adrenal cortex, testicles, thymus, small intestine, stomach, fetal brain, fetal lungs, fetal liver, and fetal kidney, obtained from Clontech, are subjected to hybridization. A [α^{32}P]dCTP-labeled X5L protein-specific DNA which lies between base pairs 1073 and 1409 of the DNA of figure 1 is used as hybridization sample. The hybridization is carried out overnight followed by wash steps under common conditions. The blots are also hybridized with a radioactive ß-actin sample for the purpose of control (cf. figure 5).

It turns out that mRNA of an X5L protein is expressed in the most varying tissues. The size of the expressed mRNA is 1.7 or 4.3 kb, which is due to differing polyadenylation signals of the DNA of figure 1. It also shows that the expression of mRNA of an X5L protein is the strongest in testicles.

(B)

An RNA *in situ* hybridization is carried out with mouse-testicle tissue. For this purpose, reference is made to the method by Wilkinson, D.G. (1992), Oxford University Press, New York. Antisense or sense RNA samples are used which correspond to base pairs 5-1169 of the DNA of figure 1.

It shows that a strong expression of mRNA of an X5L protein takes place in testicle tissue. It also turns out that the expression is limited to tubuli. At a cellular level, an expression of mRNA of an X5L protein shows in the stages of the primary and secondary spermatocytes as well as the round spermatocytes. Spermatogoniums, mature Sertoli cells and Leydig cells, however, show no expression of mRNA of an X5L protein.

Example 2: Production and purification of a spermatogenesis protein according to the invention (X5L protein)

The DNA of figure 1 is provided with BAMHI linkers subsequently cleaved using BamHI and inserted in the BamHI-cleaved expression vector pQE-8 (Quiagen company). The expression plasmid pQE-8/X5L is obtained. Such a plasmid codes for a fusion protein of 6 histidine residues (N terminus partner) and the X5L protein of figure 1 according to the invention (C terminus partner). pQE-8/X5L is used for transforming *E. coli* SG 13009 (cf. Gottesman, S. *et al.*, J. Bacteriol. 148, (1981), 265-273). The bacteria are cultured in an LB broth with 100 µg/ml ampicillin and 25 µg/ml kanamycin and induced for 4 h using 60 µM isopropyl-ß-D-thiogalactopyranoside (IPTG). Lysis of the bacteria is achieved by adding 6 M guanidine hydrochloride, and a chromatography (Ni-NTA resin) is subsequently carried out with the lysate in the presence of 8 M urea in accordance with the instructions from the manufacturer (Qiagen) of the chromatography material. The bound fusion protein is eluted in a buffer with pH 3.5. After its neutralization, the fusion protein is subjected to 18 % SDS polyacrylamide gel electrophoresis and stained using coomassie blue (cf. Thomas, J.O. and Kornberg, R.D., J. Mol. Biol. 149 (1975), 709-733).

It shows that a (fusion) protein according to the invention can be prepared in highly pure form.

Example 3: Production and detection of an antibody according to the invention

A fusion protein of Example 2 according to the invention is subjected to 18 % SDS polyacrylamide gel electrophoresis. After staining of the gel using 4 M sodium acetate an about 37 kD band is excised from the gel and incubated in phosphate-buffered common salt solution. Gel pieces are sedimented before the protein concentration of the

supernatant is determined by SDS polyacrylamide gel electrophoresis which is followed by coomassie blue staining. Animals are immunized as follows using the gel-purified fusion protein.

Immunization protocol for polyclonal antibodies in rabbits

35 µg of gel-purified fusion protein in 0.7 ml PBS and 0.7 ml of complete or incomplete Freund's adjuvant are used per immunization:

Day 0: 1st immunization (complete Freund's adjuvant)
Day 14: 2nd immunization (incomplete Freund's adjuvant; icFA)
Day 28: 3rd immunization (icFA)
Day 56: 4th immunization (icFA)
Day 80: bleeding to death.

The rabbit serum is tested in an immunoblot. For this purpose, a fusion protein of Example 1 according to the invention is subjected to SDS polyacrylamide gel electrophoresis and transferred to a nitrocellulose filter (cf. Khyse-Andersen, J., J. Biochem. Biophys. Meth. 10 (1984), 203-209). The Western blot analysis was carried out as described in Bock, C.-T. *et al.*, Virus Genes 8, (1994), 215-229. For this purpose, the nitrocellulose filter is incubated with a first antibody at 37°C for one hour. This antibody is the rabbit serum (1:10000 in PBS). After several wash steps using PBS, the nitrocellulose filter is incubated with a second antibody. This antibody is an alkaline phosphatase-coupled monoclonal goat anti-rabbit IgG antibody (Dianova company) (1:5000) in PBS. 30 minutes of incubation at 37°C are followed by several wash steps using PBS and subsequently by the alkaline phosphatase detection reaction with developer solution (36 µM 5'-bromo-4-chloro-3-indolylphosphate, 400 µM nitro blue tetrazolium, 100 mM Tris-HCl, pH 9.5, 100 mM NaCl, 5 mM $MgCl_2$) at room temperature until bands become visible.

It shows that polyclonal antibodies according to the

invention can be prepared.

Immunization protocol for polyclonal antibodies in chickens

40 µg of gel-purified fusion protein in 0.8 ml PBS and 0.8 ml of complete or incomplete Freund's adjuvant are used per immunization.

Day 0: 1st immunization (complete Freund's adjuvant)
Day 28: 2nd immunization (incomplete Freund's adjuvant; icFA)
Day 50: 3rd immunization (icFA)

Antibodies are extracted from egg yolk and tested in a Western blot. Polyclonal antibodies according to the invention are detected.

Immunization protocol for monoclonal antibodies in mice

12 µg of gel-purified fusion protein in 0.25 ml PBS and 0.25 ml of complete or incomplete Freund's adjuvant are used per immunization. The fusion protein is dissolved in 0.5 ml (without adjuvant) in the 4th immunization.

Day 0: 1st immunization (complete Freund's adjuvant)
Day 28: 2nd immunization (incomplete Freund's adjuvant; icFA)
Day 56: 3rd immunization (icFA)
Day 84: 4th immunization (PBS)
Day 87: fusion.

Supernatants of hybridomas are tested in a Western blot. Monoclonal antibodies according to the invention are identified.

Claims

1. A spermatogenesis protein, comprising the amino acid sequence of fig. 1 or an amino acid sequence differing therefrom by one or more amino acids, wherein a homology of at least 80 % exists between the latter amino acid sequence and that of fig. 1.

2. The spermatogenesis protein according to claim 1, comprising the amino acid sequence of fig. 3.

3. A DNA coding for the spermatogenesis protein according to claim 1, comprising:

(a) the DNA of fig. 1 or a DNA differing therefrom by one or more base pairs, the latter DNA hybridizing with the DNA of fig. 1 and coding for a spermatogenesis protein whose amino acid sequence has a homology of at least 80 % to that of fig. 1, or

(b) a DNA related to the DNA from (a) via the degenerated genetic code.

4. The DNA according to claim 3, wherein the DNA is that of fig. 2, fig. 3 or fig. 4.

5. An expression plasmid, comprising the DNA according to claim 3 or 4.

6. A transformant, containing the expression plasmid according to claim 5.

7. A method of producing a spermatogenesis protein, comprising the culturing of the transformant according to claim 6 under suitable conditions.

8. Antibodies directed against the spermatogenesis protein according to claim 1 or 2.

9. Use of the spermatogenesis protein according to claim 1 or 2 or a DNA according to claim 3 or 4 for studying or influencing spermatogenesis.

10. Use according to claim 9, wherein the influence of spermatogenesis comprises its activation or inhibition.

11. Use according to claim 9, wherein studying or influencing spermatogenesis comprises a diagnosis and/or treatment of disorders of spermatogenesis.

Abstract of the Disclosure

The present invention relates to a spermatogenesis protein, a DNA coding for such a protein and a method of producing such a protein. The invention also relates to antibodies directed against the protein and the use of the DNA and the protein for studying or influencing spermatogenesis.

```
        10                  30                  50                  70                  90
AGAGCCCGGGGCGAGTGGGCCTCTGCTCGTGGGTGGTTCTCGTGGAGGTCAGCTCCCGCGTGTCTCCGCTCGACAGGGTGCTTGGGCAGA

                110                 130                 150                 170
GCCCATCGGGTAGGCGCGGGCCATGGCGCAGTACAAGGGCACCATGCGCGAGGCAGGCCGTGCCATGCACCTCCTCAAGAAGCGCGAAAG
                    M   A   Q   Y   K   G   T   M   R   E   A   G   R   A   M   H   L   L   K   K   R   E   R

        190                 210                 230                 250                 270
GCAGCGGGAGCAGATGGAGGTGCTGAAGCAGCGCATCGCCGAGGAGACCATCCTCAAGTCGCAGGTGGACAAGAGGTTCTCGGCGCATTA
  Q   R   E   Q   M   E   V   L   K   Q   R   I   A   E   E   T   I   L   K   S   Q   V   D   K   R   F   S   A   H   Y

                290                 310                 330                 350
CGACGCCGTGGAGGCCGAGCTGAAGTCCAGCACGGTGGGCCTGGTGACCCTGAACGACATGAAGGCCCGGCAGGAGGCCCTGGTCAGGGA
  D   A   V   E   A   E   L   K   S   S   T   V   G   L   V   T   L   N   D   M   K   A   R   Q   E   A   L   V   R   E

        370                 390                 410                 430                 450
GCGCGAGCGGCAGCTGGCCAAGCGCCAGCACCTGGAGGAGCAGCGGCTGCAGCAGGAGCGGCAGCGGGAGCAGGAGCAGCGGCGCGAGCG
  R   E   R   Q   L   A   K   R   Q   H   L   E   E   Q   R   L   Q   Q   E   R   Q   R   E   Q   E   Q   R   R   E   R

                470                 490                 510                 530
CAAGCGTAAGATCTCCTGCCTGTCCTTTGCACTAGACGACCTCGATGACCAGGCCGACGCGGCCGAGGCCAGGCGCGCCGGAAACCTGGG
  K   R   K   I   S   C   L   S   F   A   L   D   D   L   D   D   Q   A   D   A   A   E   A   R   R   A   G   N   L   G

        550                 570                 590                 610                 630
CAAGAACCCCGACGTGGACACCAGCTTCCTGCCAGACCGCGACCGCGAGGAGGAGGAGAACCGGCTCCGAGAGGAGCTGCGCCAAGAGTG
  K   N   P   D   V   D   T   S   F   L   P   D   R   D   R   E   E   E   E   N   R   L   R   E   E   L   R   Q   E   W

                650                 670                 690                 710
GGAGGCGCAGCGCGAGAAAGTGAAGGACGAGGAGATGGAGGTCACCTTCAGCTACTGGGACGGCTCGGGCCACCCGGCGCACGGTGCGGGT
  E   A   Q   R   E   K   V   K   D   E   E   M   E   V   T   F   S   Y   W   D   G   S   G   H   R   R   T   V   R   V

        730                 750                 770                 790                 810
GCGCAAGGGCAACACGGTGCAGCAGTTCCTGAAGAAGGCGCTGCAGGGGCTGCGCAAGGACTTCCTGGAGCTGCGCGTCCGCCGGCGTGCA
  R   K   G   N   T   V   Q   Q   F   L   K   K   A   L   Q   G   L   R   K   D   F   L   E   L   R   S   A   G   V   E

                830                 850                 870                 890
GCAGCTCATGTTCATCAAGGAGGACCTCATCCTGCCGCACTACCACACCTTCTACGACTTCATCATCGCCAGGGCGAGGGGCAAGAGCGG
  Q   L   M   F   I   K   E   D   L   I   L   P   H   Y   H   T   F   Y   D   F   I   I   A   R   A   R   G   K   S   G

        910                 930                 950                 970                 990
GCCGCTCTTCAGCTTCGATGTGCACGATGACGTGCGCCTGCTCAGCGACGCCACCATGGAGAAGGACGAGTCGCACGCGGGCAAGGTGGT
  P   L   F   S   F   D   V   H   D   D   V   R   L   L   S   D   A   T   M   E   K   D   E   S   H   A   G   K   V   V

                1010                1030                1050                1070
GCTGCGCAGCTGGTACGAGAAGAACAAGCACATCTTCCCCGCCAGCCGCTGGGAGGCCTATGACCCCGAGAAGAAGTGGGACAAGTACAC
  L   R   S   W   Y   E   K   N   K   H   I   F   P   A   S   R   W   E   A   Y   D   P   E   K   K   W   D   K   Y   T

        1090                1110                1130                1150                1170
CATCCGCTAACACCCGCCTGCCAGAGCGGAAACCGGGGGTGGGGGGAGACACTCATTCTAGGCCCCATCACCAGTCACTTGATTTCGTG
  I   R   *

                1190                1210                1230                1250
ACCTTGATTTCTTCCCCCAAATTTAATAAAGACAGAGGGTTCTCATGATTCACATTGGTTGTGCTATTGCTGATGTTATGCTTTGGTTGC

        1270                1290                1310                1330                1350
TTGGTTGGTCTTTTCTGAGTATTTTAGTGTTGCCACCTGGATTTGCTGCATTGCTCTGCTGAGCTGTATTGAAACCATGACTGGGCCCAC

                1370                1390                1410                1430
TGTCAGACAGAAATTAGAATAGGAGGCACATTTTTTACCTGGTGGTTATGAGCATGGACTTGGGGGCCACAGTGACTGAGTTTGATTCCC

        1450                1470                1490                1510                1530
GACACAGCCTCCTCCTTGCTGTGTAGTTTTGGGTAAGCTTATTAAACCCCCATGCCTCAGTTTGGTCACCTGTAAAAGGAAATAACAAGA

                1550                1570                1590                1610
GCACTTACTTTATAAGATTGATGTGAGTATTAAGTGAATTAATATTTGTAAAACGCTTAGCTCTTAATAAATGTTTCTGTTGTTATTA
```

Fig. 1

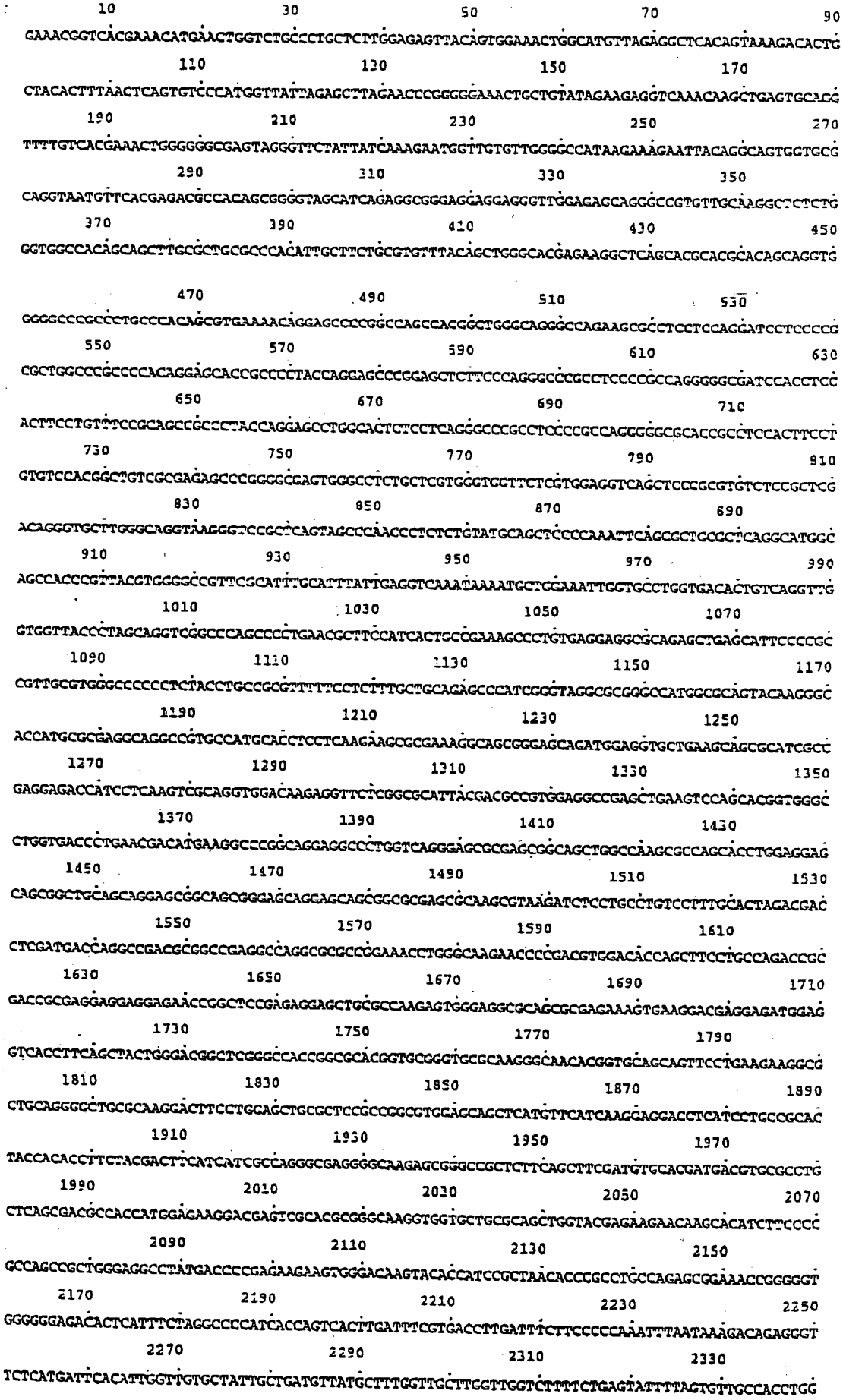

Fig. 2

Fig. 2 (cont'd)

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      2350                2370                2390                2410                2430
ATTTGCTGCATTGCTCTGCTGAGCTGTATTGAAACCATGACTGGGCCCACTGTCAGACAGAAATTAGAATAGGAGGCACATTTTTTACCT
                  2450                2470                2490                2510
GGTGGTTATGAGCATGGACTTGGGGGCCACAGTGACTGAGTTTGATTCCCGACACAGCCTCCTCCTTGCTGTGTAGTTTTGGGTAAGCTT
      2530                2550                2570                2590                2610
ATTAAACCCCCATGCCTCAGTTTGGTCACCTGTAAAAGGAAATAACAAGAGCACTTACTTTATAAGATTGATGTGAGTATTAAGTGAATT
                  2630                2650                2670                2690
AATATTTGTAAAACGCTTAGCTCTTAATAAATGTTTCTGTTGTTATTATTATGGTTTTGGTTAATTTATTTAAAGGACTGCAATGACCTA
      2710                2730                2750                2770                2790
GTTCAGAACTATTTGAGGGCAAAGGTGGACCTGCCCATCACTGGTCCCAGGATCAGCAGTTGCCAGCAGGAGGGGGCTAGCAAAGGTTGG
                  2810                2830                2850                2870
GGAGCAGCCCCCCCTCTAGTGGGCTTTAGCTGGGTTGTTTAGCCCAGAAGTTAGGAGGACAGTGAGCTAATGCAAGTAGCCTGCAG
```

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        10                  30                  50                  70                  90
ATTCGCAAAAGCACCAGAAGGAAGAGTCTTGGCTCATACATCAAAAGCTGCAGAATCTGTGAACTGACATCAGACCCAGAAGGCTACCAG

                110                 130                 150                 170
AAACAGGGACTGGGCAGGCCAAAAAGCCTTGCGCTGAACTGCAGGCATGGCGCAGTACAAAGGCACCATGCGGGAAGCTGGCCGGGCCAT
                                                    M  A  Q  Y  K  G  T  M  R  E  A  G  R  A  M

        190                 210                 230                 250                 270
GCACCTGATCAAGAAGCGTGAGAAGCAGAAGGAGCAGATGGAGGTGCTGAAGCAGCGCATCGCAGAGGAGACCATCATGAAGTCAAAAGT
 H  L  I  K  K  R  E  K  Q  K  E  Q  M  E  V  L  K  Q  R  I  A  E  E  T  I  M  K  S  K  V

                290                 310                 330                 350
GGACAAGAAGTTCTCGGCACACTACGACGCCGTGGAGGCCGAGCTGAAGTCCAGTACGGTGGGCCTGGTGACCCTGAATGACATGAAGGC
 D  K  K  F  S  A  H  Y  D  A  V  E  A  E  L  K  S  S  T  V  G  L  V  T  L  N  D  M  K  A

        370                 390                 410                 430                 450
CAAGCAGGAGGCCCTGCTGAGGGAGCGGGAGATGCAGCTGGCCAAGAGGGAGCAGCTGGAGCAACGCCGGATACAGCTGGAGATGCTGCG
 K  Q  E  A  L  L  R  E  R  E  M  Q  L  A  K  R  E  Q  L  E  Q  R  R  I  Q  L  E  M  L  R

                470                 490                 510                 530
CGAGAAGGAGCGAAGGCGAGAGCGCAAGCGCAAGATCTCCAACCTGTCTTTCACGTTGGACGAGGAAGAAGGTGACCAAGAGGACAGCCG
 E  K  E  R  R  R  E  R  K  R  K  I  S  N  L  S  F  T  L  D  E  E  E  G  D  Q  E  D  S  R

        550                 570                 590                 610                 630
CCAAGCCGAGAGTGCCGAGGCCCACAGTGCTGGAGCCAAGAAGAACTTGGGCAAGAATCCCGATGTGGACACGAGCTTCCTGCCCGACCG
 Q  A  S  S  A  E  A  H  S  A  G  A  K  K  N  L  G  K  N  P  D  V  D  T  S  F  L  P  D  R

                650                 670                 690                 710
CGAGCGCGAGGAGGAGGAGAACCGGTTGCGCGAGGAACTGCGGCAGGAGTGGGAGGCGAAGCGCGAGAAGGTGAAGGGCGAGGAGGTGGA
 E  R  E  E  E  E  N  R  L  R  E  E  L  R  Q  E  W  E  A  K  R  E  K  V  K  G  E  E  V  E

        730                 750                 770                 790                 810
GATCACCTTCAGCTACTGGGATGGCTCCGGCCACCGGCGCACGGTGCGCATGAGCAAGGGCAGCACGGTGCAGCAGTTCCTGAAGCGGGC
 I  T  F  S  Y  W  D  G  S  G  H  R  R  T  V  R  M  S  K  G  S  T  V  Q  Q  F  L  K  R  A

                830                 850                 870                 890
GCTGCAGGGGCTGCGCAGGGACTTCCGGGAGCTGCGGGCAGCGGGCGTGGAGCAGCTCATGTACGTCAAGGAGGATCTCATCCTGCCGCA
 L  Q  G  L  R  R  D  F  R  E  L  R  A  A  G  V  E  Q  L  M  Y  V  K  E  D  L  I  L  P  H

        910                 930                 950                 970                 990
CTATCACACCTTCTACGACTTCATCGTGGCCAAAGCCCGGGGCAAGAGCGGCCCGCTCTTCAGCTTCGACGTGCACGACGATGTGCGGCT
 Y  H  T  F  Y  D  F  I  V  A  K  A  R  G  K  S  G  P  L  F  S  F  D  V  H  D  D  V  R  L

               1010                1030                1050                1070
GCTGAGCGATGCCACGATGGAGAAAGATGAGTCACACGCGGGCAAGGTGGTGCTTCGCAGCTGGTACGAGAAGAACAAGCACATCTTCCC
 L  S  D  A  T  M  E  K  D  E  S  H  A  G  K  V  V  L  R  S  W  Y  E  K  N  K  H  I  F  P

       1090                1110                1130                1150                1170
TGCCAGCCGCTGGGAGCCCTACGACCCCGAGAAGAAGTGGGACAGGTACACCATCCGGTGATGCCAAGTCCCAGTTTGGGGACCTTACTC
 A  S  R  W  E  P  Y  D  P  E  K  K  W  D  R  Y  T  I  R  *

               1190                1210
CCTAACTATCGAAAATTAATAAATACAGAGGGTCCCCGTAAATCGGA
```

Fig. 3

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        10                  30                  50                  70                  90
CTAAAACCTGAAAGTTATTCTGATCAACCATACTATACCACATGCAAAATGGAGTCAGAGCTTTCTGTCTCCTCTGTAGCTAAGATCACT
                110                 130                 150                 170
AATGAGTTATTGTATGAAAAGGCAATAAAATCATGCTGTCTGGAGAGTGCCAATACTTTCAGACTAGTGTATCACGTAAACTCTTTAGTA
        190                 210                 230                 250                 270
ACAACCTACACACAAAAATTTAATCTGTAATAATCAAAGGCCCAAGTGAGCAACGACAGTCCAGGAAAACTTCATGGGAGGATTGCATTT
                290                 310                 330                 350
CAGTTGTCAGGAGATCAGACGCTGGCAGCAGGACTGCATCCATCAGTCAGTCCAAGTCGGCAGTTATACATGACCACCACCTGATTGGCC
        370                 390                 410                 430                 450
CAATCTCTGTCCTGATTGGTTAGAGCCTGCCCTAGCAGTTGGCCAATGTTTTGCATATTTTCTGTGTCAGTTAGAACAAACAATATTCGC
                470                 490                 510                 530
AAAAGCACCAGAAGGAAGAGTCTTGGCTCATACATCAAAAGGTGAGGGGACTGGCTTGAATCCAGCTGGGGCAGATGTGGGAGGTACAGC
        550                 570                 590                 610                 630
TCTTTAAACTCGAGTAAAACCAATTGTGAAGGGAGTTGAATGTTAGAGGAAAGGAATTTGTCCATTATCCTGCAAGCAGGGGAGACTAAT
                650                 670                 690                 710
GAGCCCTATCGGTGACATAATATCAACATTTTTATTGTAATTTAGGAATCACAAACTAGCAGGAAGGAGGAAGATGCCTTAAAGGGCTAT
        730                 750                 770                 790                 810
GACATATGCACTAGGAAAATAGAAATTGGGGCTTGTTCTCTCTATTGGTTGCTTTTCACTGCTGTGTCAAAAGCAACCTAAGGAGGAGGA

                830                 850                 870                 890
AAGGGTTTATTTTGATTGACTGTTTGACTCACATTTAATCCTGACAGCAAGTTGGCAGAAGCACGGAGTCATGTTGTTTCTGTAGTCAGA
        910                 930                 950                 970                 990
AAGCCGAGCAAGATAAGGACTGCGTTCATCTGCCTTTCCCTATTTCTCCTTTCTACTAGGTCTGAGACTCACGCCCATGGGCATGGTAAG
                1010                1030                1050                1070
GCCATGTTCAAGATGGTTTGTCTTTCCTCAGTTAAATCTTTCTGAAAATACTCCCACCAGACAACATGCCAAGAGCTGTGTATCCTAAGG
        1090                1110                1130                1150                1170
TTCCAAATCCTGTTAGTTGACAAGATTAACCATTACATGAGTCTCACCTCCTTAACTCAGGTCTGATACTGTTAGCTTATAGTACTGAAA
                1190                1210                1230
GCATACTGAAGGCTTCTTGTCTCTGCTAGATTGCTCTGAACTCCTCTTTTCTGCCACTGCAG
```

Fig. 4 (A)

```
        10                  30                  50                  70                  90
GAATTCAAACAAGCCAGGGAGCAGCATGAGCTTTAAAGCAGCTTGCGATATCAAAGAAAAGAAAGATGCTACGGAAATGGCGAGGAAACA
                110                 130                 150                 170
TTTAGACCTTTGGAATGACATGGAATGTCAGAGCAAAGCACTGTTTGGGAGCTATGCGGTGAAATGGTGTCCTCAGGGGAAACAAGAGGG
        190                 210                 230                 250                 270
TTTGGGGGACCAGTTTGGAGTTTGGAAAGAGTTTGATAAGAGGATGCCAGCTGTTCATGGGAATGAGAGTCCACCGAGTAAAGAAGGAGC
                290                 310                 330                 350
TACAGAAGGGTTGGGAGGCACTCGTAGAGAGCGGTCAATTCAAGTTGAGTCCAGTTAAATTAAGAGATCTCTCTTTTCCCTTGACTGAAG
        370                 390                 410                 430                 450
CACAGAGAAAACACTTTGTACTTGGCCCATCTCTGTTGCATGCAGTTCCCCTGATGTCTTGTTTCTCACGGCAAGGGAGGGAGAGCTCAG
                470                 490                 510                 530
AGTTCTTTTGTGTACTTTAGCACTGACACAAAGTGAGTTCCACTAAAACTCCATGCAAAAATCGTTCCTAAGACTTGTGCTAGGATGAAA
        550                 570                 590                 610                 630
GCTCCTTGGGATCTGCCAAGACCATAACATTAACGGGAGCTTAACCTAGCATCATCACCCTCCAGGTGCACGTAGGGGAAGCTTTCAAGG
                650                 670                 690                 710
ACTCTTTTTCTTTCCTTGCTTCTGTCCTGCAGGAGTGGGGTCCAACAAGGGCAGGTACTATCCTAAAAGGCCAACCCCCCTCATCAGGAG
        730                 750                 770                 790                 810
ACACGGTTTTCCACTTGACCCCAGCTTCACTGTGGCTAGTTCTCAGGAACCCAGGCCCAGGCTCTCTCATTGCTCTGCTCTTGCATGGCT
                830                 850                 870                 890
GTGCATGAGCAGACACGGGCAGCATGTGGTTTGCTCTGCAGACCAACCTCTACATGCAAACCCCTCAAAACCTACTGTACTAACTCAGTA
        910                 930                 950                 970                 990
GTCACATGAGGCTATCTCAGTTTGAAGTAAAATTGCTCCGTTGGTGACAGTAGTTGCATTTCAAGTACTGAGGGGCCTTCTGTGATCAGT
                1010                1030                1050                1070
AGTTACCACATCGGGTCACCCTGGAGACAGACTCATCAGAGAGGAAGCTCCATTGTAGGGCTCTGGTGTAGACCATTAATGACGCAGCTG
        1090                1110                1130                1150                1170
TACTGGTTTGATTCTCGAGCGTTTTGTTTAGTTGTTGTTTGTTTGTTTCCTAGCTGCAGAATCTGTGAACTGACATCAGACCCAGAA
                1190                1210                1230                1250
GGCTACCAGAAACAGGGACTGGGCAGGCCAAAAAGCCTTGCGCTGAACTGCAGGCATGGCGCAGTACAAAGGCACCATGCGGGAAGCTGG
        1270                1290                1310                1330                1350
CCGGGCCATGCACCTGATCAAGAAGCGTGAGAAGCAGAAGGAGCAGATGGAGGTGCTGAAGCAGCGCATCGCAGAGGAGACCATCATGAA
                1370                1390                1410                1430
GTCAAAAGTGGACAAGAAGTTCTCGGCACACTACGACGCCGTGGAGGCCGAGCTGAAGTCCAGTACGGTGGGCCTGGTGACCCTGAATGA
        1450                1470                1490                1510                1530
CATGAAGGCCAAGCAGGAGGCCCTGCTGAGGGAGCGGGAGATGCAGCTGGCCAAGAGGGAGCAGCTGGAGCAACGCCGGATACAGCTGGA
                1550                1570                1590                1610
GATGCTGCGCGAGAAGGAGCGAAGGCGAGAGCGCAAGCGCAAGATCTCCAACCTGTCTTTCACGTTGGACGAGGAAGAAGGTGACCAAGA
        1630                1650                1670                1690                1710
GGACAGCCGCCAAGCCGAGAGTGCCGAGGCCCACAGTGCTGGAGCCAAGAAGAACTTGGGCAAGAATCCCGATGTGGACACGAGCTTCCT
                1730                1750                1770                1790
GCCCGACCGCGAGCGCGAGGAGGAGGAGAACCGGTTGCGCGAGGAACTGCGGCAGGAGTGGGAGGCGAAGCGCGAGAAGGTGAAGGGCGA
        1810                1830                1850                1870                1890
GGAGGTGGAGATCACCTTCAGCTACTGGGATGGCTCCGGCCACCGGCGCACGGTGCGCATGAGCAAGGGCAGCACGGTGCAGCAGTTCCT
```

Fig. 4 (B)

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                1910                1930                1950                1970
GAAGCGGGCGCTGCAGGGGCTGCGCAGGGACTTCCGGGAGCTGCGGGCAGCGGGCGTGGAGCAGCTCATGTACGTCAAGGAGGATCTCAT
      1990                2010                2030                2050                2070
CCTGCCGCACTATCACACCTTCTACGACTTCATCGTGGCCAAAGCCCGGGGCAAGAGCGGCCCGCTCTTCAGCTTCGACGTGCACGACGA
                2090                2110                2130                2150
TGTGCGGCTGCTGAGCGATGCCACGATGGAGAAAGATGAGTCACACGCGGGCAAGGTGGTGCTTCGCAGCTGGTACGAGAAGAACAAGCA
      2170                2190                2210                2230                2250
CATCTTCCCTGCCAGCCGCTGGGAGCCCTACGACCCCGAGAAGAAGTGGGACAGGTACACCATCCGGTGATGCCAAGTCCCAGTTTGGGG
                2270                2290                2310                2330
ACCTTACTCCCTAACTATCGAAAATTAATAAATACAGAGGGTCCCCGTAAATCGGATGTGTTGGTTCTGTACCTGGCGTCATTCTTCGGT
      2350                2370                2390                2410                2430
GTTTTTAATGTTTCTGTTTGTGGCTCCTTTGTGTTCTGTGTGAAAAGGGACATGTTTTTGACTAAGTGGGTTGTGCACATTAGCTTGGTG
                2450                2470                2490                2510
GGCCAGCAGACTGGGTTTGATTTTCTTGCTCAATGTCTTACTTGTGTTGTGAGCAAAATCATTGCGGTCAATTGACTCCTTTTCCCCACC
      2530                2550                2570                2590                2610
TATACAAGGAAGTTACACCCCTTCAGGCCAGCGTGAGGAGTGAGTTAATATTTGTAAACACTTGGAACTCACTCAGTAAATGCCTGCTGT
                2630                2650                2670                2690
TTTTGTGGGCCTGGTTGCTTTACTAAAGAATGCCTACGCGATCCATCTCTGAAATGTCAAAACCAGGGTAGACCTGCATATGTCATTGGT
      2710                2730                2750                2770                2790
TTCAGGGTCAGTCGGTGCCTGAAAGCTGGTGTACAGCTTATAAGATCGGAGGCGCTTATTTTTCTTATCTTCACCCAAAGCTCACATCTA
                2810                2830                2850                2870
CATGGCAAGATTCTAAATCCCGCCCTTTAAGTTTGTATATGTTATTCATTGTTGAGTGTTTTGTTAATTTTCACTTAAAAACGTCTAAAA
      2890                2910                2930                2950                2970
TACAGTGCATCTCTTTCACGGATTTTTTTAAGTTACCCCTTTTATGTTAAAGACCAAGACTTATACTTTGGATCTCTTGCTCTGTTTCTG
                2990
GCGCTGAGTACTTGCGCCAGCCCAAGAACATGAATTC
```

Fig. 4 (B) (cont'd)

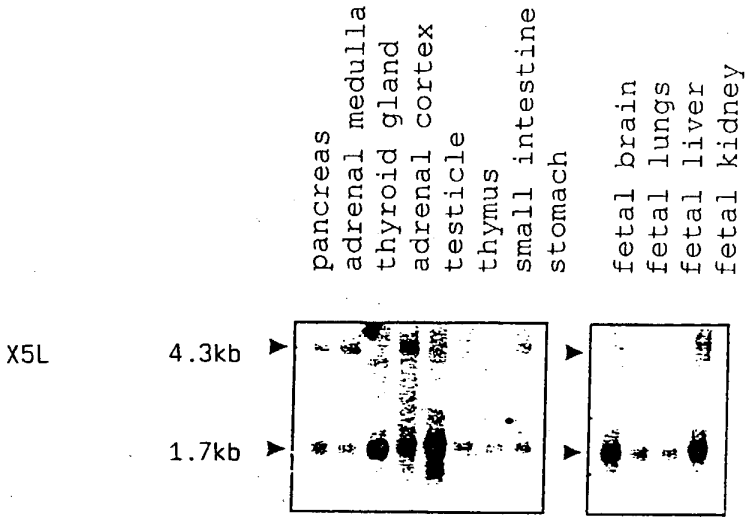
X5L
4.3kb
1.7kb
pancreas
adrenal medulla
thyroid gland
adrenal cortex
testicle
thymus
small intestine
stomach
fetal brain
fetal lungs
fetal liver
fetal kidney

Fig. 5

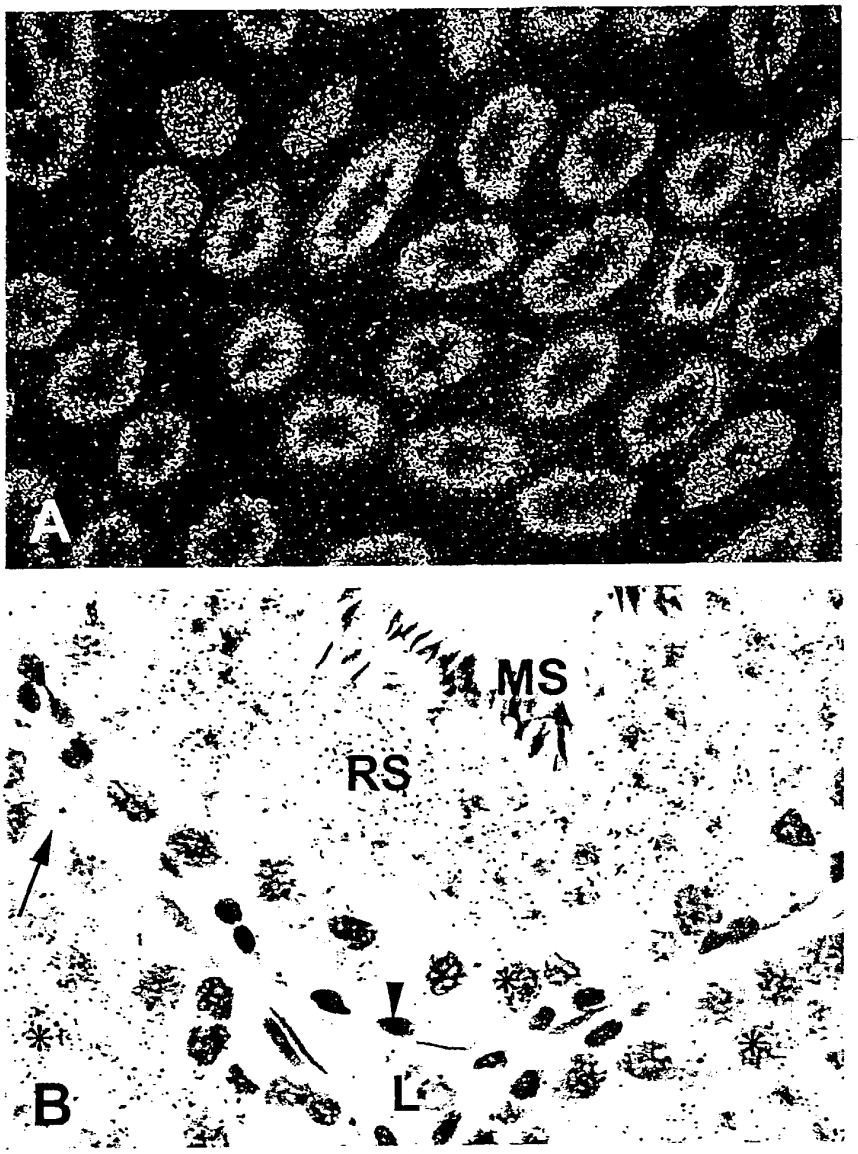

Fig. 6

K 292

P330

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION — ATTORNEY DOCKET NO. 4121-125

As a below named inventor, I hereby declare that:
My residence/post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter, which is claimed and for which a patent is sought on the invention entitled:
SPERMATOGENESIS PROTEIN
the specification of which is attached hereto unless the following box is checked:
(X) was filed on June 8, 2001 as US Application Serial No. 09/857902 or PCT International Application Number _____ and was amended on _____ (if applicable).
I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority
I hereby claim foreign priority benefits under Title 35, United States Code Section 119(a-d) or 365(b) of any foreign application(s) for patent or inventor(s) certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
Germany	198 56 882.7	10 December 1998	YES: X NO:
PCT	PCT/DE99/03972	8 December 1999	YES: X NO:

Provisional Application
I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

U.S. Priority Claim
I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS(patented/pending/abandoned)

POWER OF ATTORNEY:
As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) listed below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

2 **Steven J. Hultquist, Reg. No. 28021** **Marianne Fuierer, Reg. No. 39983**

Send Correspondence to:	Direct Telephone Calls To:
Steven J. Hultquist Intellectual Property/Technology Law P.O. Box 14329 Research Triangle Park, NC 27709	Steven J. Hultquist (919) 419-9350

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2 **Full Name of Inventor:** Zdenek Sedlacek **Citizenship:** Czech Republic

Residence: Burgstr. 52, D- 69121 Heidleberg, Germany DE

Post Office Address: Same

_____ 01.10.2001

Inventor's Signature **Date**

DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION (continued)

ATTORNEY DOCKET NO. 4121-125

D-00

Full Name of Inventor: Annemarie Poustka Citizenship: Austrian

Residence: Werderstr. 36, D-60120 Heidelberg, Germany DE Ladenburger Str. 41, 60120 Heidelberg N.P.

Post Office Address: Same

Annemarie Poustka 5.10.2001

Inventor's Signature Date

Full Name of Inventor: _____ Citizenship: _____

Residence: _____

Post Office Address: _____

_____ _____

Inventor's Signature Date

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☐ Page(s)_____ of _____ were not present for scanning. (Document title)

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